Benchmark Dose Uncertainty Analysis of Test Data

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Approach

- BMD analysis
  - Fit BMDS models
  - Record BMD_X and $BMDL_X$ (X = BMR)
  - Calculate BMDLr (BMD:BMDL ratio)
- Parametric bootstrap analysis
  - Fit selected models to original data
  - Bootstrap data from fitted responses
  - Fit selected models to bootstrap samples (1000)
  - Calculate confidence bounds from fitted parameters
  - Calculate EDLr (ED_X:EDL_X ratio)

Frambozadrine Data

Dose (mg/kg-day)	Total Number Rats	Incidence (hyperkeratosis)	Percent Response
Male			
0	47	2	4.3
1.2	45	6	13
15	44	4	9.1
82	47	24	51
Female			
0	48	3	6.3
1.8	49	5	10
21	47	3	6.4
109	48	33	69

Do we need separate dose-response relations for males and females?

Does combination alter the uncertainty in response?

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Frambozadrine: BMDS Results

Model	AIC	p-value	Deviance	BMD_{10}	$BMDL_{10}$
Male					
Multistage (2^N)	150.4	0.28	2.551	33.7	12.0
Weibull	152.3	0.12	2.478	44.5	10.8
Female					
Multistage (2^N)	142.4	0.43	1.742	34.4	21.2
Weibull	143.3	0.41	0.667	86.4	25.2
Pooled data					
Multistage (2^N)	289.0	0.60	4.498 (p = 0.98)[a]	34.1	22.9
Weibull	290.5	0.54	4.036 (p = 0.83)[b]	41.2	24.6

[a]1- pchisq(4.498 – (2.551 + 1.742), df = 3)
[b]1- pchisq(4.498 – (2.551 + 1.742), df = 3)

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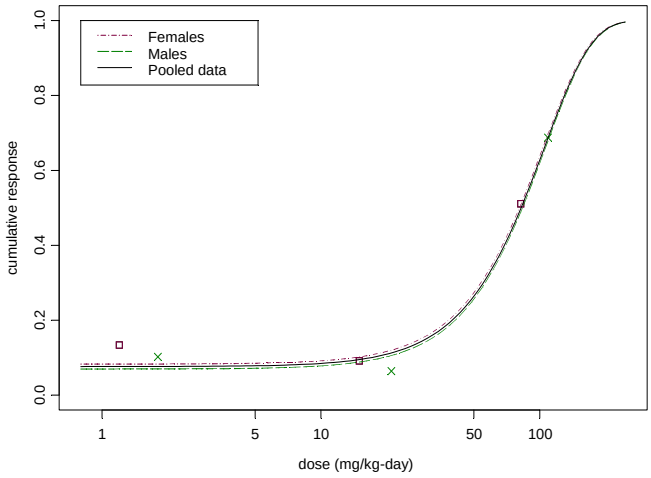
Frambozadrine:
2nd-Order Multistage Model Fits



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Frambozadrine Uncertainty Analysis
Multistage Model

BMR	BMDL	BMD	BMDLr	EDL	ED	EDLr
Male						
0.01	1.15	10.4	9.0	1.35	8.90	6.6
0.10	12.0	33.7	2.8	13.8	30.3	2.2
Female						
0.01	2.55	10.6	4.2	1.59	9.05	5.7
0.10	21.2	34.4	1.6	15.6	30.9	2.0
Pooled Data						
0.01	2.92	10.5	3.6	1.75	9.37	5.4
0.10	22.9	34.1	1.5	16.9	32.0	1.9

BMDL and EDL are lower 95% confidence bounds on the BMD_{BMR} or ED_{BMR}

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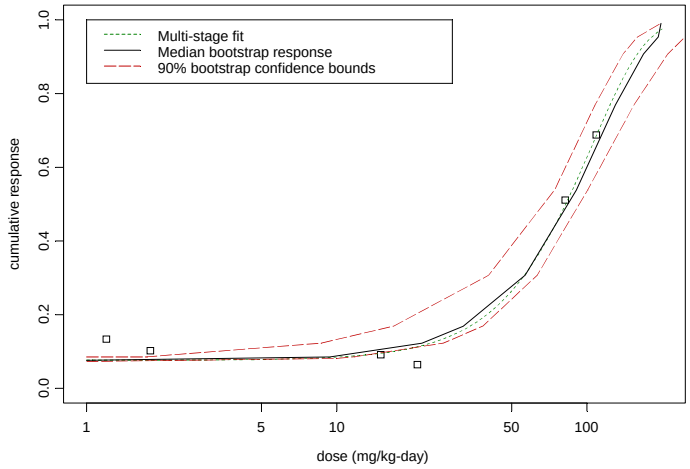
Frambozadrine: Bootstrap Confidence Bounds



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Frambozadrine Uncertainty Analysis
Weibull Model

BMR	BMDL	BMD	BMDLr	EDL	ED	EDLr
Male						
0.01	0.678	19.8	29.2	1.13	20.7	18.3
0.10	10.7	44.5	4.2	13.4	45.3	3.4
Female						
0.01	5.76	68.3	11.9	4.34	27.8	6.4
0.10	25.2	86.4	3.4	19.8	53.2	2.7
Pooled Data						
0.01	5.34	15.8	3.0	4.85	15.9	3.3
0.10	24.6	41.2	1.7	22.9	41.7	1.8

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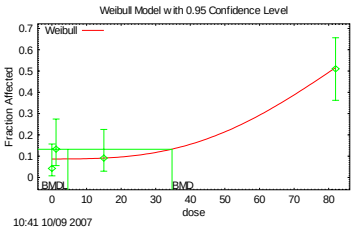
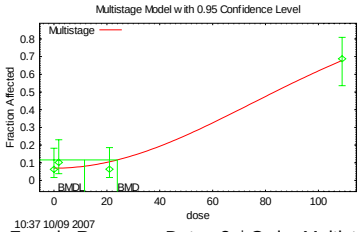
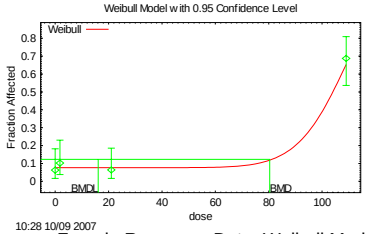
Frambozadrine Uncertainty Analysis
Weibull Plots



a. Male Response Data, Weibull Model



b. Female Response Data, 2nd-Order Multistage Model



c. Female Response Data, Weibull Model

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Frambozadrine Conclusions

- We do not need separate dose-response relations for males and females.
- Combining the response data decreases dose-response uncertainty somewhat for the multistage model and significantly for the Weibull model.
- Given the lack of response near the BMR for the female response data, however, a BMD analysis might not be appropriate. At the least, highly flexible models, such as the Weibull, probably should not be used.

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Nectorine Data

	Concentration (ppm)			
	0	10	30	60
Lesion	# response/# in trial			
Respiratory Epithelial Adenoma	0/49	6/49	8/48	15/48
Olfactory Epithelial Neuroblastoma	0/49	0/49	4/48	3/48

What is the uncertainty in response as function of dose for either respiratory epithelial adenoma OR olfactory epithelial neuroblastoma?

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Nectorine: BMDS Results

Model	AIC	p-value	BMD_{10}	$BMDL_{10}$	Multistage IUR*
Respiratory Epithelial Adenoma in Rats					
Multistage (1^N)	143.6	0.44	15.2	11.3	0.00883
Weibull	143.9	0.75	8.71	0.259	
Olfactory Epithelial Neuroblastoma in Rats					
Multistage (1^N)	55.2	0.42	70.1	39.9	0.00251
Weibull	57.2	0.24	70.4	39.9	

*$0.1/BMDL_{10}$ for the multistage model fit in units of $(mg/kg\text{-}day)^{-1}$

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Nectorine Uncertainty Analysis
Multistage Model

BMR	BMDL	BMD	BMDLr	EDL	ED	EDLr
Respiratory Epithelial Adenoma						
0.01	1.08	1.45	1.3	1.15	1.73	1.5
0.05	5.51	7.39	1.3	5.86	8.72	1.5
0.10	11.3	15.2	1.3	12.0	17.3	1.4
Olfactory Epithelial Neuroblastoma						
0.01	3.81	6.69	1.8	4.60	9.76	2.1
0.05	19.4	34.1	1.8	22.9	39.3	1.7
0.10	39.9	70.1	1.8	43.8	63.0	1.4

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Nectorine Uncertainty Analysis
Weibull Model

BMR	BMDL	BMD	BMDLr	EDL	ED	EDLr
Respiratory Epithelial Adenoma						
0.01	2.3×10^{-7}	0.191	8.4×10^{5}	4.8×10^{-5}	0.222	4600
0.05	0.0037	2.70	730	0.043	2.92	68
0.10	0.259	8.71	34	1.05	44.9	8.9
Olfactory Epithelial Neuroblastoma						
0.01	3.1×10^{-28}	6.60	2.1×10^{28}	0.094	8.43	89
0.05	2.79	34.1	12	16.3	39.9	2.4
0.10	39.9	70.4	1.8	43.2	64.4	1.5

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Nectorine Uncertainty Analysis:
Bootstrap IUR Distributions

Fractile						
0.01	**0.05**	**0.10**	**0.50**	**0.90**	**0.95**	**0.99**
Respiratory Epithelial Adenoma						
0.0033	0.0039	0.0042	0.0059	0.0079	0.0084	0.095
Olfactory Epithelial Neuroblastoma						
0.00027	0.00059	0.00080	0.0016	0.0021	0.0023	0.0027
Combined Tumors						
0.0045	0.0052	0.0056	0.0074	0.0095	0.0010	0.011

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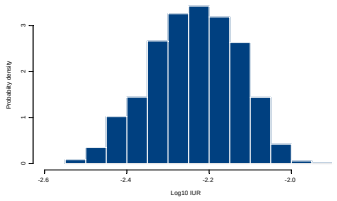
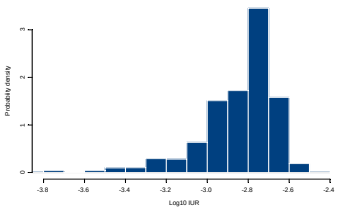
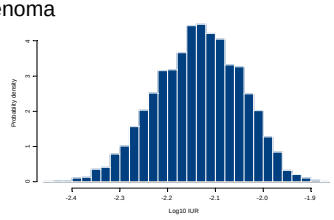
Nectorine Uncertainty Analysis:
Bootstrap IUR Distribution Plots



Respiratory Epithelial Adenoma



Olfactory Epithelial Neuroblastoma



Combined Tumors (either or)

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Nectorine Conclusions

- The constant-shape 1st-order multistage model indicates low uncertainty compared to the shape-flexible Weibull model. Assuming, however, that a mutagenic (i.e., one-hit) mode of action would apply, the Weibull model would not be considered for deriving an inhalation unit risk.
- Confidence bounds on the combined response for either tumor cannot be calculated from BMDS directly.
- Based on the 90% bootstrap confidence intervals, the uncertainty in the combined response is less than that for either of the individual tumor responses.

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Persimonate Data

	Exposure Level (ppm)	Metabolized Dose (mg/kg-day)	Survival-Adjusted Tumor Incidence	Percent Response
B6C3F1 Male Mice	0	0	17/49	34.7
	18	27	31/47	66.0
	36	41	41/50	82
Crj:BDF1 Male Mice	0	0	13/46	28.3
	1.8	3.4	21/49	42.9
	9.0	14	19/48	39.6
	45	36	40/49	81.6

Can we combine these studies?

Does it affect our uncertainty?

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Persimonate Uncertainty Analysis
Multistage Model

Model	AIC	p-value	Deviance	BMD_{10}	$BMDL_{10}$
BC63F1 Male Mice					
Multistage (1^N)	175.2	0.49	0.4714	3.70	2.71
Crj:BDF1 Male Mice					
Multistage (1^N)	242.5	0.06	5.616	3.54	2.53
Multistage (2^N)	241.6	0.10	2.673	12.2	3.45
Weibull	241.1	0.14	2.201	16.2	4.60
Pooled Data					
Multistage (1^N)	414.1	0.26	6.499 $p = 0.81$*	3.60	2.86
Multistage (2^N)	412.7	0.54	3.110	10.7	3.82
Weibull	412.7	0.54	3.103	11.5	4.27

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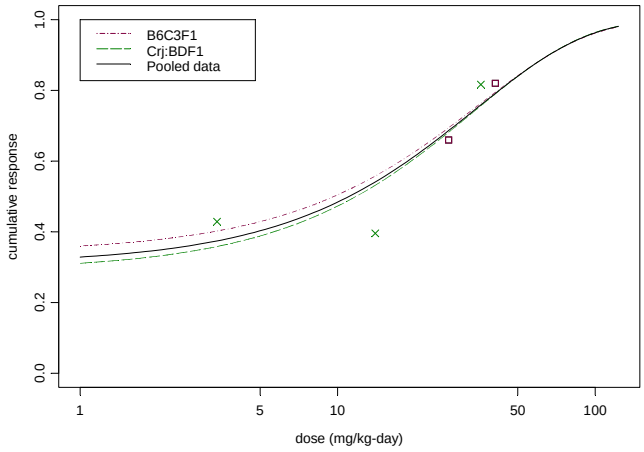
*1- pchisq(6.499 – (5.616 + 0.4714), df = 2)

Persimonate:
1st-Order Multistage Model Fits



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Persimonate Uncertainty Analysis
Multistage Model

BMR	BMDL	BMD	BMDLr	EDL	ED	EDLr
BC63F1 Male Mice						
0.01	0.259	0.353	1.4	0.249	0.348	1.4
0.10	2.71	3.70	1.4	2.61	3.65	1.4
Crj:BDF1 Male Mice						
0.01	0.242	0.338	1.4	0.237	0.336	1.4
0.10	2.53	3.54	1.4	2.49	3.52	1.4
Pooled Data						
0.01	0.273	0.343	1.3	0.270	0.344	1.3
0.10	2.86	3.60	1.3	2.83	3.61	1.3

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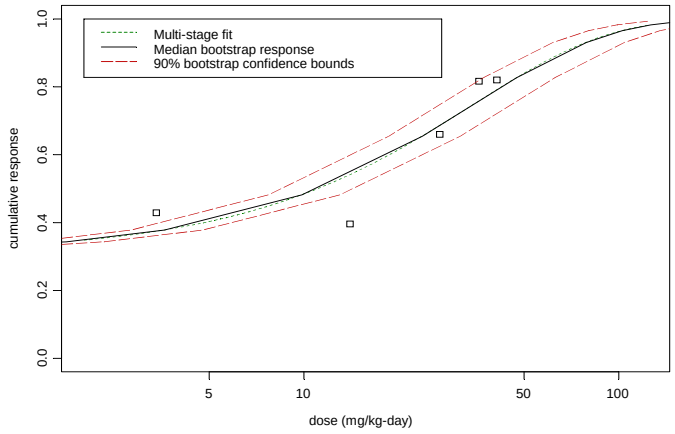
Persimonate:
Bootstrap Confidence Bounds



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Persimonate Uncertainty Analysis
Weibull Model

BMR	BMDL	BMD	BMDLr	EDL	ED	EDLr
Crj:BDF1 Male Mice [a]						
0.01	0.609	7.57	12.4	1.25	7.02	5.6
0.05	2.48	12.8	5.2	3.84	12.2	3.2
0.10	4.60	16.2	3.5	6.37	15.7	2.5
Pooled Data [b]						
0.01	0.503	3.70	7.4	0.600	3.73	6.2
0.05	2.22	8.15	3.7	2.51	8.17	3.3
0.10	4.27	11.5	2.7	4.68	11.5	2.5

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Persimonate Conclusions

- The two studies can be combined with high statistical significance.
- Combining the response data decreases dose-response does not affect the uncertainty for the 1st-order multistage model.
- Combining the response data reduces uncertainty slightly for the Weibull model based on the BMD results, but not for the bootstrap analysis.

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General Conclusions

- The BMD approach tends to overestimate (with respect to the bootstrap method) the dose-response uncertainty at low BMR values for these data, primarily for responses relatively far from the lowest observed non-background response and for smaller sample sizes.
- Overall, however, there is not too much of a difference between BMD and bootstrap results for these data.
- The Weibull model does not perform well with supralinear response data, particularly for the BMD approach and at low BMR values.